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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,953	07/11/2001	Achim H. Krotz	ISIS-4797	9234

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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	16

DATE MAILED: 06/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

F16

Office Action Summary	Application No.	Applicant(s)	
	09/902,953	KROTZ ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's response filed April 21, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed November 20, 2002 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Response to Arguments

2. Claims 1-14 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and is repeated for the same reasons of record as cited in the Office action mailed November 20, 2002.

Applicants assert that the present specification provides adequate written description for the use of the term "bioequivalents" and point to pages 38-39 as an indication that one of skill in the art would know that the term bioequivalents would include for example prodrugs, deletion derivatives, conjugates, salts, ribozymes, peptide nucleic acids, and aptamers thereof.

It is noted that the specification offers the following by way of definition:

> "**Bioequivalents**: The compositions of the present invention encompass any pharmaceutically acceptable compound that, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to "prodrugs", and "pharmaceutically acceptable salts"" of the antisense compounds of the invention and other bioequivalents" (emphasis in original).

The genus of molecules encompassed by the term "bioequivalents is thus extremely broad, because in addition to the prodrugs, deletion derivatives, conjugates, salts, ribozymes, peptide nucleic acids, and aptamers contemplated on pages 38-39 of the specification, the species that may further fall within the scope of the "bioequivalent" genus comprise any nucleic acid drug, and may even further comprise any "pharmaceutically acceptable compound that, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof". Applicants do not have adequate support for the use of such broad language, because such language encompasses an undefined and unknown number of species, included but not limited to any native protein or fragment thereof, any antibody, any small molecule inhibitor, ligand, agonist or antagonist, to name a few. In fact, as so defined, the language of "bioequivalent" potentially encompasses virtually any object of matter that interacts with any molecule in a mammal. Applicants are referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

Applicants' specification does not identify a representative number of species of compounds that are capable of providing a biologically active metabolite or residue thereof. Applicants have exemplified antisense oligonucleotides only, and have otherwise provided a list

that may include any prodrugs, deletion derivatives, conjugates, salts, ribozymes, peptide nucleic acids, and aptamers. This disclosure does not constitute a representative number of species of the extremely broad genus as required by the guidelines above. Accordingly, applicants arguments are not considered convincing, and the rejection of record is maintained.

3. Claims 1-5, 7-12, and 14 stand rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al., for the same reasons of record as cited in the Office action mailed November 20, 2002.

The claims are drawn to formulations comprising oligonucleotides with base, sugar, linkage and 2' modifications and an antioxidant in bi- or multi-phasic solutions, wherein said antioxidant partitions to the aqueous phase, and to methods of preventing desulfurization using said formulations.

Applicants have traversed the rejection of record by asserting that Zhang et al. does not anticipate the instant rejection because one of ordinary skill could not "at once envisage" applicants claimed invention from the disclosure of Zhang et al. Applicants allege that the formulations of Zhang are "numerous and diverse", and that thousands of different formulations are proposed. Applicants assert that in order to make the rejection above, that one must engage in "improper picking and choosing" of the "innumerable Zhang formulation components". Applicants liken the disclosure of Zhang et al. to a generic chemical formula that has myriad possible substituents, cite case law stating that the specific compound within the generic chemical formula must be able to be "at once envisaged" in order for a claim to be anticipated, and finally assert that one of ordinary skill could not do so from the disclosure of Zhang.

Applicants' arguments have been fully considered but they are not persuasive. It is worth noting at the outset that applicants have not argued the fact that Zhang et al. discloses all the elements of applicants claimed invention. Rather, it appears that it is applicants' conviction that while Zhang et al. does teach the elements of applicants' invention, that one of ordinary skill would not discern applicants claimed invention from the disclosure of Zhang, because Zhang et ai. discuss numerous embodiments of their invention. Thus it is applicants contention that the disclosure of Zhang et al. proposes a large enough number of variables that would force one of skill in the art to engage in "improper picking and choosing". In looking at the case law cited by applicants, it becomes clear that the disclosure of Zhang et al. does not rise to the level of improper picking and choosing as cited by applicant, because the applicants cited passages are fundamentally different than the instant situation. For example, applicants repeatedly cite that the disclosure of a genus does not anticipate the species, "since the genus would include an untold number of species". However, applicants' arguments glide over the fact that Zhang discloses both the genus *and species* claimed by applicant--not just the genus. For example, applicant is directed to the claims of Zhang et al. Claim 4 is directed to oligos specifically containing phosphorothioate modifications, as in the instant claims. Claim 11 of Zhang further claims an oligo in a pharmaceutical carrier, which the specification stipulates may be an emulsion that contains antioxidants, as instantly claimed. For example, from Zhang et al. (col. 15, lines 35-42):

> "Antioxidants are also commonly added to emulsion formulations to prevent deterioration of the formulation. Antioxidants used may be free radical scavengers such as tocopherols, alkyl, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin."

Thus, while applicants are correct in implying that a genus does not anticipate a species, applicants are incorrect in implying that Zhang et al. does not disclose the instantly claimed species. Although Zhang et al. indeed discusses various embodiments of their invention, it is also clear that they provide guidance in teaching embodiments that anticipate applicants' claimed invention, and further, that the cited case law demonstrating that a genus does not anticipate a species is irrelevant to the instant rejection.

Since the claims clearly direct one of skill to a phosphorothioated oligonucleotide in a combination with a pharmaceutically acceptable carrier, and since the specification clearly states that such a pharmaceutically acceptable carrier may comprise emulsions that commonly contain antioxidants of the type claimed by applicants, one or ordinary skill in the art could "at once envisage" applicants claimed invention from Zhang et al. In summary, the teachings of Zhang et al. would have led one of ordinary skill in the art to the instantly claimed invention via the claims of Zhang.

Furthermore, in attempting to cite case law discussing how a generic chemical formula with infinite variation is somehow analogous to the teachings of the Zhang patent, applicant has failed to properly consider more pertinent passages from the M.P.E.P. that render moot this strained comparison. Applicants' arguments assert that because Zhang et al. discloses many possible embodiments of their invention, one of ordinary skill in the art would not be able to discern applicants invention without engaging in "improper picking and choosing" However, such a term was coined for describing that a generic chemical formula with See for example M.P.E.P. § 2131.02:

"A REFERENCE THAT CLEARLY NAMES THE CLAIMED SPECIES ANTICIPATES THE CLAIM NO MATTER HOW MANY OTHER SPECIES ARE NAMED":

> "A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. Ex parte A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (The claimed compound was named in a reference which also disclosed 45 other compounds. The Board held that the comprehensiveness of the listing did not negate the fact that the compound claimed was specifically taught. The Board compared the facts to the situation in which the compound was found in the Merck Index, saying that "the tenth edition of the Merck Index lists ten thousand compounds. In our view, each and every one of those compounds is described' as that term is used in 35 U.S.C. § 102(a), in that publication."). Id. at 1718. See also In re Sivaramakrishnan, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982) (The claims were directed to polycarbonate containing cadmium laurate as an additive. The court upheld the Board's finding that a reference specifically naming cadmium laurate as an additive amongst a list of many suitable salts in polycarbonate resin anticipated the claims. The applicant had argued that cadmium laurate was only disclosed as representative of the salts and was expected to have the same properties as the other salts listed while, as shown in the application, cadmium laurate had unexpected properties. The court held that it did not matter that the salt was not disclosed as being preferred, the reference still anticipated the claims and because the claim was anticipated, the unexpected properties were immaterial.).

Thus even, for the sake of argument, if the claims and specification of Zhang et al. does not lead one of ordinary skill in the art to applicants claimed invention, the present invention is still anticipated, because Zhang et al. clearly disclose all the elements of applicants claimed invention, because from Sivaramakrishnan,

> "The Board held that the comprehensiveness of the listing did not negate the fact that the compound claimed was specifically taught."

This section of the M.P.E.P. was cited in a previous Advisory notice; applicants' response was to assert that this citation was irrelevant, because, applicants maintain, the case cited therein (*In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA) 1982) is not analogous. In support, applicants cite that the court upheld the rejection of the claims on appeal, which recited a polycarbonate resin containing a cadmium laurate additive, because the anticipating reference of "Gable discloses a chemical mixture of "***only*** two ingredients, polycarbonate and a metallic salt" (emphasis from applicants arguments). This is clearly misleading. Gable actually claims a compound comprising two generic ingredients, however,

numerous species of these genii were listed in the specification--it was precisely this aspect that was at issue, i.e. whether Gable's listing which "broadly discloses numerous suitable metals and anions [in the specification], so that a large number of salts are subsumed under the generic formula (*Sivaramakrishnan , supra*)" actually conferred anticipation to the two generic ingredients as claimed in Gable, and thus whether Gable constituted prior art under 35 U.S.C. § 102(b). The court determined that although two genii were claimed, that it did constitute prior art under 35 U.S.C. § 102(b).

In summary, despite applicants arguments that "Zhang provides ***no direction whatsoever*** (emphasis from applicants arguments)", Zhang **directly claims** several of the elements of applicants' invention (phosphorothioated oligonucleotides, in a pharmaceutically acceptable diluent), and otherwise directs one of ordinary skill to the remainder of the elements by clearly stating that it is normal to include anti-oxidants of the type claimed by applicants in such formulations. Accordingly, Zhang et al. is considered to anticipate the claims as outlined above, and the rejection of said claims under 35 U.S.C. § 102(b) is maintained.

Claim Rejections - 35 USC § 103

4. Applicant's arguments, filed April 21, 2003, with respect to the rejection of claims 1-14 under 35 U.S.C. § 103(a) as being obvious over have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground of rejection is made under 35 U.S.C. 103(a).

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. in view of Demopoulos et al. (U.S. Patent Number 6,204,248). The new ground of rejection renders moot some of applicants' arguments; however, those elements of applicants' arguments considered to be relevant to the instant rejection are addressed below.

The claims of the instant invention are drawn to formulations comprising oligonucleotides with base, sugar, linkage and 2' modifications and an antioxidant in bi- or multi-phasic solution, wherein said antioxidant partitions to the aqueous phase, or methods of preventing desulfurization wherein said antioxidant is added to said formulation.

Zhang et al. teach and claim antisense compounds comprising phosphorothioate, base, sugar, linkage or 2' modifications. Furthermore, Zhang et al. claim antisense compounds comprising pharmaceutically acceptable carriers or diluents, wherein said diluent may be an emulsion that contains antioxidants.

Demopoulos et al., teach the use of glutathione to protect against oxidation during induction, transription, translation, or post-translational modification of macromolecules such as nucleic acids, and further teach that α-lipoic acid and cysteine are also effective antioxidants.

It would have been obvious to one of ordinary skill in the art to use glutathione, α-lipoic acid, or cysteine in the antioxidant-containing emulsions of Zhang et al. One of ordinary skill in the art would have been motivated to create such emulsions, because Zhang et al. expressly teaches and claims phosphorothioated oligonucleotides and pharmaceutical combinations, and further teaches that one of ordinary skill commonly adds antioxidants to emulsions to reduce the breakdown of the active ingredients. One of ordinary skill in the art would have had a reasonable expectation of making such oligonucleotides and antioxidant-containing emulsions to prevent

oxidation, since since the use of antioxidants is well known in the pharmaceutical art as demonstrated by Zhang et al. Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious at the time the invention was made.

Applicant traversed the previous rejection of the above claims as being obvious, on the grounds that none of the references teach the use of water-soluble antioxidants over other antioxidants. Since there can only be two types of solubities, it is assumed that applicants are stating that none of the references teach the advantage of using water-soluble antioxidant vs. using oil-soluble antioxidants. Applicant argues that while the references disclose the use of several different antioxidants in biphasic micellar solution, that they do not disclose the advantage of using water-soluble antioxidants over the use of oil soluble antioxidants. However, since Zhang et al. expressly teaches the use of a water-soluble antioxidant as instantly claimed, the use of a water-soluble anti-oxidant is considered to be anticipated by Zhang et al. as outlined above. The instant obviousness rejection is directed to the limitations comprising the specific antioxidants of the claim set, rather than the generic claim of water-soluble antioxidants in biphasic solution with oligonucleotides. Therefore, no motivation is required to reject, since it is not being rejected under 35 U.S.C. § 103(a). The same is true with applicants' argument that there is no motivation in Zhang that would lead one of ordinary skill to select phosphorothioate modifications over any other modification presented in Zhang et al. As stated above, claim 4 of Zhang et al. specifically claims phosphorothioate compounds to the exclusion of other compounds. The fact that the reference specifically claims phosphorothioated compounds is considered to be a strong teaching toward the use of such phosphorothioated oligonucleotides.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
June 25, 2003

KAREN LACOURCIERE
PATENT EXAMINER